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(57) Abstract

Disclosed is a contraceptive regimen of the progestogen–only type. Good cycle–control and contraceptive efficacy is obtained by providing a progestogen phase of 21–25 days and a placebo or pill–free phase of 1–7 days. The daily dosage of the progestogen is in an amount sufficient to achieve contraceptive working on the basis of ovulation inhibition.

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PROGESTOGEN-ONLY CONTRACEPTIVE KIT

The invention pertains to a contraceptive kit (drug delivery system) comprising means for the daily administration of a progestogen as the single active substance, i.e. a contraceptive regimen of the progestogen-only type.

Contraceptive regimens of the progestogen-only type ("progestogen-only pill' or "POP") are known. Thus, in EP 491 443 it has been disclosed that by selecting desogestrel or 3-ketodesogestrel as the progestogen at certain specified dosages administered over an entire menstrual cycle, complete ovulation inhibition is achieved. This POP works well, and is marketed under the tradename Cerazette®. Another available POP is with levonorgestrel 30 μg per day, e.g. Follistrel® and others.

Such POPs have the advantage of avoiding the administration of estrogens, but have a high incidence of bleeding at irregular intervals (menstrual spotting or break through bleeding). With such POPs it is also quite common that amenorrhoea occurs, especially after a longer period of use. For many women, the occurrence of bleeding during tablet intake as well as the occurrence of amenorrhoea are disconcerting since they are interpreted as signs that the contraceptive working is absent, and is thus not generally desired. Major improvements have been proposed, according to which periodically an anti-progestogen is administered, which leads to bleeding patterns that more closely resemble the natural menstrual cycle. Although this is not disadvantageous, it requires the administration of yet another active substance, viz. the anti-progestogen. It is an object of the present invention to provide a POP which mimics the natural cycle, while minimising the number of medicinally active substances to which the user is exposed.

Besides the above se modern, available POPs, long ago several other POPs have been proposed. Thus, in FR 2,223,018 a contraceptive regimen is disclosed in which on the fifth day of the menstrual cycle a woman receives 0.40 mg of norethindrone, and this is given daily for seven days. The dosage is increased to 0.8 mg norethindrone for the next seven days, and to 1,50 mg norethindrone for yet another seven days. Thereafter seven days without the administration of an active agent follows, and then the 0,40 mg norethindrone phase recommences. This contraceptive

regimen has not become commercially available, and suffers from a very high dose of progestogen.

In US 3,822,355 a contraceptive regimen has been disclosed in which during the first twelve to sixteen days of the menstrual cycle a placebo is administered, the next four days a daily dose of 2-20 mg of a progestogen such as norethindrone. This high dosage serves to inhibit the function of the *corpus luteum*. The remainder of the cycle a dosage of 10-40% of the previous progestogen dosage is administered. In an example, the respective dosages are 5 mg and 1 mg, which makes the progestogen-burden unacceptably high.

It should be noted that these old suggestions to use increased daily dosages of progestogen are known to reduce the pregnancy rates, but such an increase in dosage also increases the frequency of intermenstrual bleeding (i.e. "spotting"), which is clearly not desired. E. Diczfalusy et al, Progestogens in Therapy, p. 150 (Raven Press, NY 1983). In the art of contraception, these old, high dosage POP concepts have been abandoned.

In a recent disclosure, EP 641 565, it has been proposed to use (halo)melatonin as a contraceptively active agent in conjunction with a progestogen. In this regimen, suppression of the hypothalamic-pituitary-ovarian (HPO) axis and inhibition of ovulation are mainly attributed to the melatonin, which is given for 28 days (i.e. continuously). The progestogen, which is administered for 23 days, is described as secondary. It possibly serves to induce a withdrawal bleeding and to provide back-up contraception.

According to the present invention it has now been found that, surprisingly, a pill-free or placebo interval can be introduced into a continuous POP of the type described in EP 491 443, i.e. a regimen in which a progestogen is the single active substance. Thus, the contraceptive kit according to the invention provides for a phase of 21-27 days on which a progestogen is administered daily in the same, ovulation-inhibiting daily dosage, and a placebo or pill-free phase of 1-7 days. This finding, that contraception by means of specifically a full ovulation-inhibiting effect can be obtained in a regimen having a placebo or pill-free interval and without the co-administration of an estrogen, was found with the very progestogen employed in EP 491 443, desogestrel, but the principle of the invention holds for other progestogens as well, and preferably

for other potent progestogens such as (17α)-17-hydroxy-11-methylene-19-norpregna-4,15-diene-20-yn-3-one (hereinafter referred to as Org 30659) and gestodene. During the placebo or pill-free interval, a withdrawal bleeding will occur. This indicates the contraceptive working and ensures a good cycle control with minimised spotting.

The present regimen is surprisingly simple and efficacious, and is fundamentally different from the POPs known in the art. As compared to continuous POPs, the unexpected possibility of a placebo or pill-free interval provides for a menstrual cycle which mimics the natural cycle. As compared to the old, abandoned POPs in which a pill-free or placebo period is provided, the choice of a single, ovulation inhibiting daily dosage makes for a lower progestogen burden.

The invention includes a drug delivery system for contraceptive use containing sequential daily (oral) dosage units in two sets, the first set comprising 21-27 units each of which contain a progestogen in an ovulation-inhibiting amount, the second set comprising 1-7 units not containing an active substance (placebo dosage units). It is possible that only the first set is present. In that case, in the place of the placebo tablets of the second set, the package of the kit will contain the instruction not to take pills or other dosage units for 1-7 days. It should be noted that, also in the case of the placebo units being absent, the kit according to the present invention is markedly distinct from the kit described in EP 491 443, which explicitly provides for the uninterrupted daily administration of desogestrel.

In order to most ideally mimic the natural menstrual cycle, it is preferred that the total number of days in the regimen of the invention is 28.

Basically all progestogens commonly used for contraception can be employed in the present invention, provided that the ovulation-inhibiting dose is not pharmaceutically unacceptable for other reasons. The person skilled in the art is aware of the required doses, which are approximately as follows: at least 0.5 mg/day for norethindrone (norethisterone), at least 0.06 mg/day for desogestrel and Org 30659, at least 0.1 mg/day for levonorgestrel and at least 0.04 mg/day for gestodene. Preferably, the daily dosage units contain a progestogen selected from the group consisting of desogestrel, Org 30659, levonorgestrel, and gestodene, in an amount equivalent in ovulation-inhibiting activity with 70-90 μg desogestrel (about 45-60 μg gestodene).

The two phases of the contraceptive regimen of the invention are preferably such that the placebo or pill-free phase is as short as possible, while retaining a withdrawal bleeding. Thus the preferred kits and drug delivery systems of the invention have 24-25 daily dosage units of the progestogen, and a placebo or pill-free interval of 3-4 days.

The progestogen is incorporated into dosage units for oral administration. The term "dosage unit" generally refers to physically discrete units suitable as unitary dosages for humans, each containing a predetermined quantity of active material calculated to produce the desired effect, for instance tablets, pills, powders, suppositories, capsules and the like.

Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, conventional techniques for making tablets and pills, containing active ingredients, are described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture).

For making dosage units, e.g. tablets, the use of conventional additives, e.g. fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used in the one or more of the compositions.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like used in suitable amounts. Lactose is a preferred carrier. Mixtures of carriers can also be used.

A process of manufacturing the kit of the invention comprises mixing predetermined quantities of progestogen with predetermined quantities of excipients and converting the mixture into dosage units containing the progestogen.

A preferred process of manufacturing the pharmaceutical product according to the invention involves incorporating the desired dosages of contraceptive steroid, for example desogestrel,

etonogestrel (which is also known as 3-ketodesogestrel), or mixtures thereof into tablets by techniques such as wet granulation tableting techniques.

The invention also includes a pharmaceutical product (i.e. the dosage units or the package containing the dosage units), a method of using the product, and a process of manufacturing the pharmaceutical product.

The invention also includes a method of providing contraception involving administering to a woman the above-mentioned regimens.

The invention is further explained by the following illustrative examples.

Example I

Coated tablets intended for once daily administration were made having the composition:

Ingredient	Amount (mg/tablet)
desogestrel	0.075
corn starch	6.500
povidone	1.950
stearic acid	0.650
colloidal silicone dioxide	0.650
dl-α-tocopherol	0.080
lactose	qsad 65.000

Coating layer (filmcoat-dry) ingredient:	Amount (mg/tablet)
hydroxypropylmethylcellulose	0.75
polyethylene glycol 400	0.15
titanium dioxide	0.1125
talc	0.1875

Example II

Tablets analogous to those of Example I were made with Org 30659 in four doses, viz. 0.06 mg. 0.12 mg, 0.18 mg and 0.24 mg.

Example III

The tablets of Examples I and II were tested in 77 healthy female volunteers in a non-public, double-blind randomised study. Upon 21 days of administration, ovulation was completely inhibited in all women with all doses used, including in 13 women that received 0.075 mg desogestrel and 15 women that received 0.060 mg Org 30659.

Claims:

1. A contraceptive kit comprising means for the daily administration of a progestogen as the sole contraceptively active substance, characterised in that the kit provides for a phase of 21-27 days on which a progestogen is administered daily in the same, ovulation-inhibiting dosage, and a placebo or pill-free phase of 1-7 days.

2. A contraceptive kit according to claim 1, characterised in that the progestogen is selected from the group consisting of desogestrel, Org 30659, levonorgestrel, and gestodene, in an amount equivalent in ovulation-inhibiting activity with 70-90 µg desogestrel.

3. A contraceptive kit according to claim 2, characterised in that the progestogen is gestodene in a daily dosage of 60 µg.

4. A contraceptive kit according to claim 2, characterised in that the progestogen is desogestrel in a daily dosage of 75 µg.

5. A contraceptive kit according to any one of the preceding claims, characterised in that the progestogen phase comprises 24-25 daily dosage units and the placebo or pill-free phase is 3-4 days.

6. A drug delivery system for contraceptive use containing sequential daily dosage units, characterised by containing a first set comprising 21-27 units each of which contain a progestogen in an ovulation-inhibiting amount, and a second set comprising 1-7 units not containing an active substance (placebo dosage units).

7. A drug delivery system according to claim 6, characterised in that the progestogen is selected from the group consisting of desogestrel, Org 30659, levonorgestrel, and gestodene, in an amount equivalent in ovulation-inhibiting activity with 70-90 µg desogestrel.

8. A drug delivery system according to claim 6 or 7, characterised in that the first set comprises 24-25 dosage units and the second set 3-4 dosage units, the total being 28.